

# PATENT SPECIFICATION

(11) 1340516

1340516

## NO DRAWINGS

(21) Application No. 56709/70 (22) Filed 30 Nov. 1970  
(61) Patent of Addition to No. 1340515 dated 30 Nov. 1970  
(44) Complete Specification published 12 Dec. 1973  
(51) International Classification C08B 21/26//27/22  
(52) Index at acceptance  
C3F 324 326 330 335 431 43Y 440 451 452 471 544  
54X 55Y 57X 626 723 727  
C3R 27C16 27C21 27C29 27C2A 27C6X 27C8P 27C8R  
27L2X 27L5D

(72) Inventor BILLY F. RANKIN



## (54) OPHTHALMIC SOLUTION

(71) We, BURTON PARSONS CHEMICALS, INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 7351, 86th 5 Avenue, Washington, District of Columbia, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly 10 described in and by the following statement:—

The present invention relates to a multi-functional ophthalmic solution designed for and adapted to general use in the eyes of 15 humans and domestic animals, and is a modification of the invention claimed in our copending Application No. 56708/70 (Serial No. 1340515), which discloses and claims ophthalmic compositions and their use; these 20 compositions are generally similar to those of the present application except that they contain no cellulosic derivatives.

The ophthalmic solution of the present 25 invention may be used to provide a synthetic mucous layer which serves as a wetting agent in the eye (i.e. an artificial tear material useful for the treatment of both "dry-eye" or as a cleaning, lubricating, and cushioning agent for the eye after an injury or therapeutic surgery), as a carrier for ophthalmic medicaments, and as a cleaning, lubricating, and cushioning agent for both hard and gel-type contact lenses.

Heretofore, ophthalmic solutions have 35 generally conformed to the general specifications required for all such intended utilizations in the treatment of the eye. Such solutions have generally been isotonic, buffered to the required pH, and sterile, and 40 have contained additives for improved viscosity and longer retention in the eye. However, with many such known solutions, the problems of dosage, irritation to the eye, stability, and ocular response persist.

45 Many attempts have been made to resolve

these problems by modifying existing formulas, using different forms of eye-treating substances, or using bases immiscible with aqueous solutions. Such attempts have added little to the performance qualities of the products.

It is accordingly an object of the present invention to provide a multipurpose ophthalmic solution, suitable for general utilization in the eye of both humans and domestic animals. A further object of the present invention is the provision of such solutions which can be readily modified for particular purposes and utilizations, including the provision of a wetting agent, which serves as an artificial tear for the treatment of "dry-eye", or a cushioning or lubricating agent for an injured or surgically treated eye, as a cleaning, lubricating and cushioning agent for utilization in conjunction with both hard and gel-type contact lenses, and the like.

Accordingly, this invention provides an ophthalmic composition comprising an aqueous solution of a ethylene oxide polymer having a molecular weight of at least 100,000 in an amount sufficient to provide a viscosity of up to 30,000 cps., up to 5000 wt.%, based on the said polymer, of a polyalkylene glycol, and at least one water-soluble ophthalmically acceptable cellulosic derivative, and no ophthalmic medicament as hereinafter defined.

This invention also provides a method of wetting a contact lens comprising immersing the lens in an ophthalmic composition as defined above

The invention further includes within its scope a contact lens, especially a gel-type contact lens, whenever in contact with an ophthalmic composition as defined above.

The invention further provides a method of treating the eye in non-human animals which comprises contacting the eye with an ophthalmic composition as defined above.

Finally, the invention provides a method

50

55

60

65

70

75

80

85

90

of cushioning a contact lens, especially a gel-type contact lens, in contact with the human eye, which comprises maintaining between the eye and the lens a film of an ophthalmic composition as defined above.

The term "ophthalmic medicament" as used in this specification means a substance having a positive prophylactic or curative effect when applied to the eye; it includes substances with a physiological action (such as pilocarpine) and antibiotics (such as penicillin) but not substances with a mere antiseptic, biocidal or preservative action (such as thiomersal).

Our copending application No. 33488/73, (Serial No. 1340518), divided out of this application, discloses and claims ophthalmic compositions generally similar to those of the present invention, except that they contain an ophthalmic medicament as hereinbefore defined. Our copending Application No. 33487/73 (Serial No. 1340517) divided out of No. 56708/70 (Serial No. 1340515) discloses and claims ophthalmic compositions generally similar to those of No. 56708/70 except that they contain an ophthalmic medicament as defined therein.

Polyethylene oxide is known to exhibit excellent lubricating characteristics in aqueous solution and is freely soluble in water without degradation or hydrolysis. Wide ranges of molecular weights are available, and in the present invention can be from 100,000 up to several million, e.g. 5,000,000 or even greater. The higher molecular weight materials are preferred in the present invention, and a range of 3,000,000 to 5,000,000 has been found particularly useful. Most preferred is a polyethylene oxide having a molecular weight of about 4,000,000. Such resins have extraordinary thickening action in water, even in the presence of salts. The thickening power increases sharply with both concentration and molecular weight. Thus, to attain the desired viscosity, substantially less ethylene oxide polymer is required when the relatively higher molecular weights are used than would be the case when a lower molecular weight polymer is utilized. In addition, the higher molecular weights result in a higher strength lubricating film in solutions owing to orientation of polymer molecules. The concentration of the ethylene oxide polymer will vary in the present invention with the molecular weight to provide a viscosity of from 0 to about 30,000 cps at 20°C. as measured by Brookfield Viscometer, where viscosities of from 0 to about 200 cps are measured using the ultra low viscosity adaptor rotated at a speed of 0.6 rpm, and viscosities greater than about 200 cps are measured with a number 6 spindle rotated at 10 rpm. Such viscosities will ordinarily be obtained when the concentration is within the range of about .05 to 2.0 weight per cent, depending upon the molecular weight of the polymer employed. With lower viscosities, whether due to lower molecular weight polymers or lower concentration, or both, inferior lubrication results, while higher viscosities result in difficult handling properties and characteristics, including insufficient flowability for full effective utilization in the eye.

The high molecular weight ethylene oxide polyethers utilized in the composition and methods of the present invention can be conveniently prepared in the presence of a catalyst and an organic diluent in which the ethylene oxide monomer is soluble and the polymeric product is insoluble. During polymerization, the polymer chain grows through addition of the ethylene oxide monomer to a hydroxyl-terminated polyether molecule derived from previously reacted monomer units. The resultant materials are granular, tough, water soluble polymers which can range in molecular weight for about 10,000 to 5,000,000 or even more. The specific techniques for producing these polymers are well-known to the art and form no part of the present invention.

Aqueous solutions of the polyethylene oxide resins have a low level of oral toxicity and very good compatibility with the skin or in the eye. They are also characterized by high level of pituitousness and an extraordinarily high degree of pseudo-plasticity. The solutions are highly stable through a wide range of temperatures and can tolerate extremely wide variations in pH. Since the resins are non-ionic, their solutions undergo predictable salting effects and the inclusion of salts depresses the upper temperature limit of solubility and tends to reduce solution viscosities. The salting-out effect is mild in comparison with that observed in the case of poly-electrolytes, but is comparable with that observed with other neutral molecules dissolved in high dielectric media. As a consequence, solutions of relatively low concentration of resin, on the order of those contemplated in the present invention, can tolerate substantial amounts of both organic and inorganic salts.

Because of the strong hydrogen-bonding affinity of the ether oxygen in the polyethylene oxide chain, the resin solutions will form association complexes with a wide variety of materials. Such association complexes *per se* often exhibit properties markedly different from either component alone, but it has been found that the resin will give up associated materials when introduced into the eye. The dissociation *in vivo* may result from a salting out effect produced by the materials with which the solutions are contacted, e.g. various salts occurring in tears and the like.

Because of the high levels of pseudo-plasticity and pituitousness of polyethylene

oxide aqueous solutions, it is necessary to include in the solution a material which will render a plasticizing effect. In addition, it is also desirable to include a humectant which will enhance fluid retention over the course of long term usage in the eye. These functions are provided by the inclusion in the solution of a polyalkylene glycol. The preferred polyalkylene glycol is polyethylene glycol, such as the Carbowaxes (the word "Carbowax" is a Registered Trade Mark), as supplied by Carbide and Carbon Chemicals Company. Such materials have molecular weights ranging from about 400 up to as much as about 6000. Particularly preferred in the compositions of the preferred invention is polyethylene glycol having molecular weight of about 4000, although this preference is primarily because of the ready availability and convenience of processing of the particular material. Polyglycols containing other alkylene groups can also be utilized, such as polypropylene glycols and the like, but such materials are often not readily available, and for this reason alone are not particularly preferred in the present invention. The polyalkylene glycol can be present in amounts ranging up to 5000 preferably 500 to 5000, weight per cent based on the weight of the ethylene oxide polymer. Less than about 100% by weight can result in insufficient water retention and plasticizing effect, with concomitant drying of the eye and irritation of ocular tissue, while amounts greater than about 5000 weight per cent can exhibit a "salting out" effect, with the formation of waxy solid globules or particles which can be irritating to ocular tissue.

Ophthalmically compatible cellulose derivatives, of a variety soluble in water, such as, for example, methyl cellulose, hydroxy-ethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, and the like are, according to the invention, included in the aqueous solution to act as a mechanical buffer or as a viscosity controlling agent, and can be used to maintain the viscosity of the overall composition within the desired range as hereinbefore described. Specifically, the cellulose derivatives should be present in an amount sufficient to maintain viscosity of the overall composition at the desired level.

The basic ophthalmic solution of the present invention, i.e. the aqueous solution of polyethylene oxide, polyalkylene glycol, and cellulosic derivative, is useful *per se* in a number of contexts. Primary among these is the provision of a synthetic mucous layer, which serves to clean and lubricate the eye, serving as a wetting agent and artificial tear for the treatment of "dry-eye" or to provide a cushioning and lubricating effect in an injured or surgically treated eye. A related effect is the cleaning, lubricating, and cushioning effects attained when the solution of the present invention is used in conjunction with contact lenses, of both the hard resin and gel type. Representative of the problems generally applicable to each of the foregoing usages, is the use of the ophthalmic base solution of the present invention in conjunction with gel-type contact lenses, and accordingly the use of the solution will be discussed with the particular reference thereto.

The advent of the gel contact lens has generated entirely new requirements for contact lens treating solutions, and entirely new problems in hygenic handling and care for the lenses. In contrast to the more common hard type lens, usually made of polymethylmethacrylate, the gel lens will absorb relatively large proportions of water to form a soft, pliable material which has a tendency to fray. The gel is a three-dimensional lattice formed by the polymerization of glycol esters and diesters of acrylic acids. The glycol moieties of the molecules impart a strongly hydrophilic character to the lattice with the consequent ability to absorb rather large amounts of water. By utilizing the unique properties of these lenses, new therapeutic options are presented for the treatment of ocular debilities. Since the lens *per se* represents only the environment of use of the composition, a more complete discussion of its physical parameters need not be repeated here. A discussion of the gel contact lens, including both the preparation and use thereof, occurs in "Augenoptika" (published Vienna), Heft 6, 1964, pages 5 and 6, which reports a paper delivered by Maximilian Dreyfus at the 15th WVA annual meeting.

One characteristic peculiar to the gel lens is the requirement that treating solutions contain no component that can become entrained in the lattice of the gel, since such materials tend to accumulate and become irritating to the ocular tissue. The lens does, however, require a cleaning and lubricating solution to cushion the ocular tissue from direct contact with the lens. The requirement for a cleaning action is shared by the gel-type lens with hard lenses and with synthetic tears and other such ophthalmic solutions. The exposure of the eye to various atmospheric pollutants, such as smoke, dust, pollen, noxious and irritating gases and the like can create severe discomfort and irritation, particularly in situations where the pollutants collect in the natural or artificial tear film to persist for substantial periods of time to exert their irritating effects. In addition to the avoidance of material which can accumulate in the gel, the materials used must be compatible with the gel and with ocular tissue, and not interfere with the physio-chemical balance of the precorneal films.

Another surprising aspect of the composition of the present invention is the bactericidal effect which has been observed, both *in vitro* and *in vivo*, with a number of bacteria, particularly confirmed with *Bacillus subtilis*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The reasons for such activity remain at present unclear and are not fully understood, and accordingly, no explanation for such activity can be offered at present.

In addition to the *per se* usefulness of the ophthalmic solution of the present invention, the ophthalmic solution of the present invention finds an additional broad area of use as a carrier for ophthalmic medicaments, particularly those requiring an acid pH. Such use is the subject of our copending application No. 33488/73 (Serial No. 1340518).

It is sometimes necessary for ophthalmic compositions to be maintained at particular pH, and, in these instances, one or more pH buffers such as sodium borate is added to maintain a solution of a neutral or slightly basic pH. Typically, the buffering substances present in an amount sufficient to maintain the pH at the desired level, are from between about 7.4 and about 8.2, and preferably at about 7.6. Other buffering compositions can be used as well, including a combination of phosphates such as, for example, mono-sodium phosphate and disodium phosphate to provide both acid and base control. Other phosphates, acetates, and carbonates can be substituted for the phosphates mentioned above, provided they are compatible with the eye. A preferred combination is phosphoric acid and sodium borate. Specifically the amount of buffering additions can range from about 0 to 4%, preferably about 0.2%, for the dibasic component, and from about 0 to about 0.5% for the mono-basic component, where the percentages are by weight based upon the total weight of the overall composition, with the ratio of components balanced to provide proper pH for the overall composition.

The composition of the invention can also contain one or more eye compatible biocides, such as thiomersal (sodium ethylmercurithiosalicylate otherwise known as thimerosal), and the di-, tri-, or tetrasodium ethylenediamine tetraacetates. The percentages of such biocides can vary over a broad range, but typically do not exceed about 1% by weight of the overall composition.

In addition, the composition of the present invention can also contain one or more eye compatible non-ionic surfactants in amounts varying over a wide range, but typically in amounts up to about 0.5% by weight, in order to provide product stability. An example of the surfactants which can be utilized are Tergitol 1559 (Carbide and Carbon Chemicals Co.); Pluronic F68 (Wyandotte

Chemical Corp., Michigan Alkali Division); Tweens of H.L.B. value of 11 or higher (Atlas Powder Company). [The words "Tergitol," "Pluronic" and "Tween" are Registered Trade Marks].

Still another subsidiary component which can be added to the ophthalmic solutions of the present invention includes polyvinyl pyrrolidone (such as Plasdene C, supplied by Enira Chemicals, Division of GAF Corp.) which performs a number of desirable functions. Polyvinyl pyrrolidone (PVP) acts as a detoxicant, binding anti-toxins present in eye fluids, and rendering them harmless. PVP also acts to protect the solution by preventing its breakdown because of particle agglomeration, and acts as a demulcent lubricant by a combination of adhesive and lubricating properties which aid in the spreading of the viscous solution. The PVP also operates to prevent blepharospasm (involuntary eyelid contraction), but has little effect on an overall composition viscosity. PVP is desirably present in an amount of from 0.5 to 10.0, preferably from 0.5 to 5, weight per cent based on the overall solution. For the purposes of this invention PVP is not considered to be an ophthalmic medicament.

The foregoing illustration of secondary additives for the ophthalmic solution of the present invention is intended to be merely exemplary of the more common of the additives to ophthalmic solutions well-known to those of ordinary skill in the art. It should accordingly be understood that such additives are not required for effective operation of the ophthalmic solution of the present invention, and nor is it intended by the enumeration of certain additives to exclude others.

While the ophthalmic solution of the present invention is readily formed by simply combining the ingredients, the polyethylene oxide material can occasionally present difficulties in readily dissolving. Such difficulties can be avoided by the utilization of the following techniques. An increment of distilled water sufficient to dissolve the constituents of the composition is placed in a stainless steel container and heated to about 50°C. If a surfactant is included in a composition, it is dissolved first in distilled water by agitation, e.g. with a dispersing mixer which has a variable speed control set at low speed.

The polyalkylene glycol (such as Carbowax 4,000) and other additives (such as biocides), pH buffers and the like are then dissolved with medium speed agitation in the water/surfactant mixture, following which the polyvinyl pyrrolidone is added with high-speed mixing and agitation. The cellulosic derivative mechanical buffer is sifted slowly into the vortex created by the agitator at high speed. When the cellulosic substance is com-

pletely dispersed, the ethylene oxide polymer, such as Polyox Resin WSR 301, is sifted slowly into the vortex at high agitation, until the resin appears to be climbing up the agitator shaft, at which time the speed is reduced to 100 to 200 rpm. Agitation is then continued until the resin is completely dispersed in the solution, typically from 2 to 6 hours. Additional distilled water is then added to bring the solution up to volume. Because the resin can be precipitated out at high temperatures, the product may be sterilized, after packaging by means of ethylene oxide gas sterilization. Containers for the solution are placed in racks in a gas autoclave, which draws a vacuum of about 24 mm of mercury, after which all air is replaced with an ethylene oxide-Freon mixture (12—88%) at 12 psi for 12 hours, and at relative humidity of 45 to 50%. (The word "Freon" is a Registered Trade Mark). It is also possible to sterilize in an autoclave if the conditions are controlled to minimize particle agglomeration of any resin which precipitates out. So long as agglomeration is not excessive, the resin will redissolve when the temperature is again reduced. Even when autoclaving temperatures are extreme and the time at temperature causes excessive agglomeration, the resin will redissolve, but at a slower rate.

#### EXAMPLE

As an illustration of the composition of the present invention the following composition was prepared on a large scale:

35	bactericide (thiomersal, 10%)	240 c.c.
	disodium phosphate	1200 grams
	polyethylene glycol (MW. 4,000)	6000 grams
40	polyvinyl pyrrolidone	30000 grams
	disodium ethylenediamine-tetracetate	600 grams
	non-ionic surfactant	132 grams
45	hydroxy ethyl cellulose (MW 52,000)	3000 grams
	polyethylene oxide (MW 4,000,000)	3000 grams
	distilled water	150 gallons (U.S.)

The solution formed from the foregoing components was clear and free of polymer globules, and was found to have a pH of about 7.3 and a viscosity of about 150 cps.

The solution was utilized as a wetting, cleaning, and cushioning medium by a number of patients using hard-type, polymethyl methacrylate contact lenses. With patients who had previously worn the lenses, greater comfort and tolerance was reported, even by those who had previously experienced difficulty with the lenses. Most patients reported that they were able to wear their lenses for greater periods of time than

had previously been possible, regardless of the type of wetting solution they had used before. With patients who had not previously worn contact lenses, the solution of the present invention dramatically reduced the problems of lens delivery and greatly accelerated the adaptation of the patients to the use of the lenses. In all the trials, no adverse side effects or irritation was noted either subjectively or by clinical examination.

It has been noted that in the utilization of the ophthalmic solution of the present invention with contact lenses, certain ranges of viscosity provide better results than others. For example, with hard-type lenses, the best results are attained at a viscosity of about 30 to 200 cps, and that range is accordingly preferred for such usage. The most preferred viscosity for use with hard-type lenses is about 150 cps. With the gel-type lens, the most effective, and hence the preferred viscosities lie in the range of about 0 to 30 cps, with values of about 10 being most preferred. No variation of effectiveness with viscosity has been noted when solution is used as a carrier for medicaments or as a synthetic tear or the like.

It should be noted that a viscosity of zero as measured is a result of the limitations of the available techniques and apparatus, and does not represent such an anomaly as it might superficially appear. It should further be noted that all designations of viscosity appearing herein represent the values as obtained with the Brookfield Viscosimeter, where all values below 200 are obtained with the ultra low viscosity adapter rotated at 0.6 rpm and all values above 200 are obtained with a number 6 spindle at 10 rpm. For values ranging from about 175 to about 250 cps, results obtained by the two differing adaptations are generally comparable in the case of the present solutions.

A further example of the effectiveness of the composition of the present invention occurs primarily in the area of ophthalmologic diagnosis, where it is conventional to apply fluorescein, or a comparable material, dissolved in a carrier, to the eye and after allowing the dye to penetrate the tissues of the eye, to conduct an examination by visual inspection with the aid of an ultra-violet light source, which causes the dye to fluoresce. It has been found that when the ophthalmic solution of the present invention is utilized as the carrier, the dye is absorbed in substantially greater proportions and at a much faster rate than has been possible with the compositions of the prior art. Accordingly, solutions of fluorescent dyes in the ophthalmic solution of the present invention are of great aid in the examination of the eye.

Any use of the invention as defined in the following claims for the medical treatment

65

70

75

80

85

90

95

100

105

110

115

120

125

of the human body is hereby disclaimed. Subject to the above disclaimer, what we claim is:—

1. An ophthalmic composition comprising an aqueous solution of an ethylene oxide polymer having a molecular weight of at least 100,000 in an amount sufficient to provide a viscosity up to 30,000 cps., up to 5,000 wt.%, based on the said polymer, of a polyalkylene glycol, at least one water-soluble ophthalmically acceptable cellulosic derivative, and no ophthalmic medicament as hereinbefore defined.
2. The composition of claim 1 in which the cellulosic derivative is selected from methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carbomethyl cellulose, hydroxy-propyl methyl cellulose, and a mixture of two or more of these substances.
3. The composition of claim 1 or 2 in which the ethylene oxide polymer has a molecular weight of 3,000,000 to 5,000,000.
4. The composition of claim 2 in which the ethylene oxide polymer has a molecular weight of about 4,000,000.
5. The composition of claim 1, 2 or 3 in which the polyalkylene glycol has a molecular weight of from 400 to 6000.
6. The composition of any preceding claim in which the polyalkylene glycol is polyethylene glycol.
7. The composition of claim 6 in which the polyethylene glycol has a molecular weight of about 4,000.
8. The composition of any of claims 1 to 5 in which the polyalkylene glycol is polypropylene glycol.
9. The composition of any preceding claim that contains from 500 to 5000 wt.% of polyalkylene glycol.
10. The composition of any preceding claim in which the concentration of ethylene oxide polymer is from 0.5 to 2.0 wt.%.
11. The composition of any preceding claim in which the aqueous solution has a pH of from 3 to 7.
12. The composition of claim 11 comprising boric acid.
13. The composition of any of claims 1 to 12 in which the aqueous solution has a basic or neutral pH maintained by an eye-compatible pH-buffer.
14. The composition of claim 13 in which the pH is from 7.4 to 8.2.
15. The composition of claim 14 in which the said pH is about 7.6.
16. The composition of claim 13, 14 or 15 in which the buffer comprises phosphoric acid and sodium borate.
17. The composition of claim 13, 14 or

15 in which the buffer is a combination of mono-sodium and di-sodium phosphates.

18. The composition of any of claims 13 to 17 in which the buffer comprises a monobasic component and a dibasic component, the dibasic component being present in an amount of up to 4.0 wt.%, and the monobasic component being present in an amount of up to 0.5 wt.%, based on the total weight of the composition.

19. The composition of any preceding claim in which the aqueous solution further comprises up to 1 wt.% of an eye-compatible biocide.

20. The composition of any preceding claim in which the aqueous solution further comprises up to 0.5 wt.% of an eye-compatible non-ionic surfactant.

21. The composition of any preceding claim in which the aqueous solution further comprises from 0.5 to 5 wt.% of polyvinyl pyrrolidone.

22. The compositions of claim 1 that are hereinbefore specifically described in the Example.

23. A method of wetting a contact lens comprising immersing the lens in an ophthalmic composition of any of claims 1 to 22.

24. The method of claim 23 in which the lens is a gel-type lens.

25. The method of claim 23 substantially as hereinbefore described or exemplified.

26. A contact lens whenever in contact with an ophthalmic composition of any of claims 1 to 22.

27. The contact lens of claim 25 which is a gel-type contact lens.

28. The contact lens of claim 25 substantially as hereinbefore described or exemplified.

29. A method of treating the eye in non-human animals which comprises contacting the eye with an ophthalmic composition of any of claims 1 to 22.

30. The method of claim 29 substantially as hereinbefore described or exemplified.

31. A method of cushioning a contact lens in contact with the human eye which comprises maintaining between the eye and the lens a film of the composition of any of claims 1 to 22.

32. The method of claim 31 in which the lens is a gel-type lens.

33. The method of claim 31 substantially as hereinbefore described or exemplified.

For the Applicants,  
**CARPMAELS & RANSFORD,**  
 Chartered Patent Agents,  
 43, Bloomsbury Square,  
 London, WC1A 2RA.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.  
 Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
 which copies may be obtained.